Cochrane Library

Cochrane Database of Systematic Reviews

Oxcarbazepine add-on for drug-resistant partial epilepsy (Protocol)

Atim-Oluk M, Jackson CF, Marson AG

Atim-Oluk M, Jackson CF, Marson AG.
Oxcarbazepine add-on for drug-resistant partial epilepsy.
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD012433.
DOI: 10.1002/14651858.CD012433.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Oxcarbazepine add-on for drug-resistant partial epilepsy

Margaret Atim-Oluk[1], Cerian F Jackson[2], Anthony G Marson[2]

[1]South Wales Deanery, Swansea, UK. [2]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Contact address: Cerian F Jackson, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Clinical Sciences Centre for Research and Education, Lower Lane, Fazakerley, Liverpool, L9 7LJ, UK. cjacks@liv.ac.uk.

Editorial group: Cochrane Epilepsy Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2017.

Citation: Atim-Oluk M, Jackson CF, Marson AG. Oxcarbazepine add-on for drug-resistant partial epilepsy. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD012433. DOI: 10.1002/14651858.CD012433.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the efficacy and tolerability of oxcarbazepine when used as an add-on treatment for patients with drug-resistant partial epilepsy.

BACKGROUND

Description of the condition

Epilepsy is a disease arising from an enduring and pathological excessive discharge of a set of neurons in the brain, clinically characterised by recurrent unprovoked epileptic seizures or in the context of an epilepsy syndrome. There are many causes, alongside several clinical and electroencephalographic manifestations that can result in epilepsy (Fisher 2014). The condition is associated with considerable physical, cognitive, psychiatric and psychological comorbidity (LaFrance 2008; Burton 2012).

Epilepsy is common worldwide; a meta-analysis of 65 studies estimated lifetime prevalence in high-income countries as 5.8 per 1000 whereas in resource-poor countries the estimate was 10.3 per 1000 and 15.4 per 1000 in urban and rural areas, respectively (Bell 2014).

The United Kingdom General Practice Study of Epilepsy found 60% of epilepsies to be convulsive, of which around two-thirds comprise partial seizures or partial with secondary generalisation (Sander 1990; Shorvon 2014).

Epilepsy is commonly treated with antiepileptic drugs (AEDs) with many patients rendered seizure free. Unfortunately, an estimated 30% of epilepsy cases are resistant to conventional AED regimens and can require several agents to control seizures (Cockerell 1995; Kwan 2000), especially partial seizures which originate from one area of the brain (Panebianco 2015). Drug resistant epilepsy is defined as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (ILAE 2009). There are also non-medical interventions for epilepsy available such as vagal nerve stimulation or surgery (Panebianco 2015; West 2015).

The present review will focus upon the effects of oxcarbazepine on seizures, side effects, cognition and quality of life when used as an add-on treatment for patients with drug-resistant partial epilepsy.

Description of the intervention

Oxcarbazepine is an analogue of carbamazepine. Oxcarbazepine is thought to have certain advantages over carbamazepine. In particular, there are fewer side effects and the dose can be titrated to

a therapeutic dose more quickly (Grant 1992). Oxcarbazepine is an AED used as monotherapy for children and adults with partial onset seizures. It is associated with level A and level D evidence for efficacy and effectiveness for children and adults, respectively (Glauser 2013).

How the intervention might work

AEDs have numerous modes of action. They aim to target neuronal receptors in order to either reduce neuronal excitation or increase inhibition, thus deceasing the likelihood of seizure discharges (NICE 2012). Oxcarbazepine has been shown to exert antiepileptic activity by blockade of voltage-dependent sodium channels in the brain. Based on in vitro and in vivo findings and compared with antiepileptic drugs such as carbamazepine, phenytoin and phenobarbital, oxcarbazepine has a low propensity for drug-drug interactions (Flesch 2004). However the drug is metabolised hepatically, being rapidly reduced by cytosolic enzymes in the liver to its monohydroxy derivative (MHD), which is responsible for the pharmacological effect of the drug. Therefore oxcarbazepine could potentiate other AEDs that are metabolised hepatically. At oxcarbazepine doses above 1.2g, a 40% increase in the concentration of phenytoin and a 15% increase in phenobarbital levels were observed. Furthermore,oxcarbazepine is associated with decreased clearance with moderate to severe renal impairment. Therefore dose adjustments are necessary in situations of AED polypharmacy or moderate to severe renal impairment (Flesch 2004).

Why it is important to do this review

A large amount of evidence has been accrued regarding the efficacy and tolerability of new AEDs. The International League against Epilepsy and other organisations have produced guidelines on how to select new AEDs (Kang 2012). New AEDs have been tested and used with success, mainly as add-on therapies to standard drugs such as phenytoin, carbamazepine and valproate. The majority of trials investigating add-on therapy with AEDs have recruited patients with partial epilepsy (experiencing simple partial and/or complex partial and/or secondary generalised tonic-clonic seizures; Commission 1989) that have been resistant to antiepileptic drug treatment.

The introduction of several new AEDs means that systematic reviews are needed to determine their effect as add-on agents for people with partial seizures. These reviews will help inform clinicians on the best add-on agents to use for their patients (Marson 1997; Privitera 1999). Therefore we present a systematic review of oxcarbazepine as an add-on treatment in drug-resistant epilepsy.

OBJECTIVES

To assess the efficacy and tolerability of oxcarbazepine when used as an add-on treatment for patients with drug-resistant partial epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the review studies need to meet the following criteria:

1. randomised controlled trials (RCTs), including quasi-randomised trials in which the method of allocation concealment is inadequate;
2. double, single or unblinded trials;
3. placebo-controlled or active-controlled studies;
4. parallel group or cross-over studies. For cross-over studies, we plan to use the first treatment period as a parallel trial.

Types of participants

Adults and children with drug-resistant partial epilepsy, as defined by The International League Against Epilepsy (ILAE 2009). Participants who have undergone other interventions to treat epilepsy, such as surgery, vagal nerve stimulation or ketogenic diet, will be included.

Types of interventions

1. The active treatment group received therapy with oxcarbazepine in addition to their usual treatment.
2. The control group received a placebo, an alternative antiepileptic drug or a different dose of oxcarbazepine in addition to their usual treatment.

Types of outcome measures

Primary outcomes

(1) Median percentage seizure reduction per 28 days

The median percentage seizure reduction every 4 weeks in the treatment period compared to the pre-randomisation baseline period. This outcome is commonly reported in this type of study, and can be calculated for studies that do not report it, provided that baseline seizure data were recorded.

(2) Fifty per cent or greater reduction in seizure frequency

The proportion of patients with a 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period. This outcome is commonly reported in this type of study, and can be calculated for studies that do not report it, provided that baseline seizure data were recorded.

(3) Adverse effects

The proportion of patients experiencing any of the following side effects:

1. Ataxia
2. Dizziness
3. Fatigue
4. Nausea
5. Somnolence
6. Headache
7. Hyponatraemia
8. Vertigo
9. Diplopia
10. Rash
11. Tremor
12. Pyrexia
13. Abnormal gait
14. Abdominal pain
15. Nystagmus
16. Viral infection
17. Vomiting
18. Abnormal vision
19. Any other adverse event

Secondary outcomes

(1) Seizure freedom

The proportion of patients with an 100% reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period. This outcome is commonly reported in this type of study and can also be calculated in studies that do not report it, provided that baseline seizure data were recorded.

(2) Treatment withdrawal

The proportion of patients withdrawing from the treatment during the course of the treatment period was chosen as a measure of 'global measure of tolerability'. In studies of relatively short duration, treatment is unlikely to be withdrawn due to lack of efficacy and any treatment withdrawal is likely due to side effects.

(3) Cognitive effects

At present, there is no consensus as to which instruments should be used to assess the effects of AEDs on cognition. As a result the assessment of cognitive effects is likely to be approached in a heterogeneous way (Cochrane 1998).

(4) Quality of life

Once again, there is no consensus as to which instruments should be used to assess this and we expect to see significant heterogeneity in the outcome measures used.

Search methods for identification of studies

Electronic searches

We will search the following databases. There will be no language restrictions.

- Cochrane Epilepsy Group Specialized Register using the search strategy set out in Appendix 1.
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO) using the search strategy set out in Appendix 2.
- MEDLINE (Ovid) 1946 to present using the search strategy set out in Appendix 3.
- ClinicalTrials.gov using the search terms: oxcarbazepine AND epilepsy.
- WHO International Clinical Trials Registry Platform (ICTRP) using the search terms: oxcarbazepine AND epilepsy NOT NCT*.

Previously SCOPUS was searched as an alternative to EMBASE, but this is no longer necessary, because randomised and quasi-randomised controlled trials in EMBASE are now included in CENTRAL.

Searching other resources

References from published studies

We will review the reference lists of retrieved studies to search for additional reports of relevant studies.

Efforts to identify unpublished studies

Unpublished data will be sought from Novartis (the manufacturer of oxcarbazepine). The results of the identified unpublished studies will be compared with results from published studies to assess the presence of publication bias.

Other

We will ask colleagues if they are aware of any studies that we may have missed.

Data collection and analysis

Selection of studies

Two review authors (CJ and MA) will independently assess the titles and abstracts identified from the searches and exclude any irrelevant studies. The same two authors will then review the full-text papers for inclusion. Any disagreements will be resolved by mutual discussion and if necessary the opinion of a third author (AGM).

Data extraction and management

The same review authors will extract the following information from included trials (again, any disagreements will be resolved by mutual discussion).

Methodological trial design

(a) Method of concealing randomisation.
(b) Method of blinding.
(c) Whether any patients had been excluded from reported analyses.
(d) Duration of baseline period.
(e) Duration of treatment period.
(f) Dose(s) of oxcarbazepine tested and potential comparator AED treatment type and dose.

Patient/demographic information

(a) Number of patients allocated to each treatment group.
(b) Age/sex.
(c) Seizure types.
(d) Seizure frequency during baseline period.
(e) Number of background drugs.

Where necessary, original authors will be asked to confirm the following:
(a) the method of randomisation;
(b) the total number of patients randomised to each group;
(c) the number of patients in each group achieving a 50% or greater reduction in seizure frequency per treatment group;
(d) the number of patients having treatment withdrawn post randomisation per treatment group.

For those excluded:
(a) the reason for exclusion;
(b) whether any of those excluded completed the treatment phase;
(c) whether any of those excluded had a 50% or greater reduction in seizure frequency during the treatment phase.

Outcomes

The number of patients experiencing each outcome (see Types of outcome measures) will be recorded per randomised group.

Assessment of risk of bias in included studies

Two review authors (MA, CJ) will independently assess the risk of bias for each trial in accordance with the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements will be discussed and if necessary the opinion of a third review author (AGM) will be sought. Studies will be rated as having a high, low or unclear risk of bias for six domains applicable to RCTs: randomisation sequence, allocation concealment, blinding, incomplete data outcome, selective outcome reporting and other sources of bias. We will also assess the potential impact of outcome reporting bias by including an Outcome Reporting Bias in Trials (ORBIT) table in the review (Kirkham 2010).

Measures of treatment effect

For dichotomous outcomes such as seizure reduction, seizure freedom, adverse effects and treatment withdrawal we plan to report risk ratios (RRs) using 95% confidence intervals.

If it is possible to combine continuous outcomes, such as cognitive effects and quality of life, in a meta-analysis, ideally we plan to report the mean difference. However as we expect to see significant variability, we plan to report the standardised mean difference (SMD). In the event that there is significant heterogeneity of outcome measures and meta-analysis is deemed to be inappropriate, we plan to report the results of these outcomes narratively.

Unit of analysis issues

In the event that cross-over trials are included in this review, we plan to include results from the first arm of the trial in meta-analyses. However, if these data are not available and the cross-over trial has used adequate methodology (for example, sufficient wash-out periods), we plan to carry out a generic inverse variance meta-analysis to combine data.

If trials have more than one treatment arm (for example, different doses of oxcarbazepine versus a control group), the treatment groups will be combined for meta-analysis and the dosage effects will be reported narratively.

In trials with more than one treatment arm, using two different AEDs, we will complete two comparisons; one comparing oxcarbazepine with the placebo and one comparing oxcarbazepine with the other treatment.

Dealing with missing data

In the event of missing data, reasons for this will be sought by contacting study authors in order to conclude whether data are missing at random or not.

Assessment of heterogeneity

Clinical and methodological heterogeneity will be assessed visually by two authors (MA, CJ) independently. We expect to see some differences in control groups, outcome measures and time scales. We do not expect significant clinical or methodological heterogeneity to the degree to which meta-analysis would be inappropriate.

The same two authors plan to assess visually the clinical and methodological heterogeneity of the included studies, and plan to use an I^2 statistic and a Chi^2 test where applicable to assess statistical heterogeneity. We judge a Chi^2 P value of less than 0.1 and I^2 greater than 50% to indicate statistical heterogeneity.

Assessment of reporting biases

We plan to request protocols from study authors and investigate outcome reporting bias using the ORBIT matrix system (Kirkham 2010).

To examine publication bias, we will search for unpublished data by carrying out a comprehensive search of multiple sources and requesting any unpublished data from study authors. We also plan to look for small study effects to establish the likelihood of publication bias.

Data synthesis

Ideally we plan to combine data in a fixed-effects meta-analysis. However, where there is significant clinical, methodological or statistical heterogeneity, we will combined data in a random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

Where possible, we will stratify subgroup analysis by: type of control group, clinical sample (adults or children), duration of treatment, treatment dose and number of concomitant AEDs.

Sensitivity analysis

In the event of any peculiarities or inconsistencies being identified, we will carry out a sensitivity analysis. To do this, we will include only studies rated as having low risk of bias in a second meta-analysis and results from this will be compared to the overall meta-analysis.

Summarising and interpreting results

We will use the GRADE approach to interpret findings (Schunemann 2011). We will use GRADE Profiler Software (GRADEPro 2004), and import data from Review Manager 5 (RevMan 2014), to create 'Summary of findings' tables for each comparison included in the review for the primary outcomes.

The 'Summary of findings' table for each comparison will include information on overall quality of the evidence from the trials and information of importance for healthcare decision making. The GRADE approach determines the quality of evidence on the basis of an evaluation of eight criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, presence of plausible confounding that will change effect and dose-response gradient). We will use these to guide our conclusions and recommendations.

ACKNOWLEDGEMENTS

We thank the Cochrane Epilepsy Group for their support in the development of this review.

REFERENCES

Additional references

Bell 2014
Bell GS, Neligan A, Sander JW. An unknown quantity - the worldwide prevalence of epilepsy. *Epilepsia* 2014;**55**(7): 958–62.

Burton 2012
Burton K, Rothgathe J, Whittaker RG, Mankad K, Hunter E, Burton MJ, et al. Co-morbidity of epilepsy in Tanzanian children: a community-based case-control study. *Seizure* 2012;**21**(3):169–74.

Cochrane 1998
Cochrane HC, Baker GA, Chadwick DW. Neuropsychological outcomes in randomized controlled trials of antiepileptic drugs: a systematic review of methodology and reporting standards. *Epilepsia* 1998;**39** (10):1088–97.

Cockerell 1995
Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. *Lancet* 1995;**346**(8968): 140–4.

Commission 1989
Commission on classification and terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**(4):389–99.

Fisher 2014
Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;**55**(4):475–82.

Flesch 2004
Flesch G. Overview of the clinical pharmacokinetics of oxcarbazepine. *Clinical Drug Investigation* 2004;**24**(4): 185–203.

Glauser 2013
Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al. ILAE Subcommission on AED Guidelines: updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2013;**54**(3):551–63.

GRADEPro 2004 [Computer program]
Brozek J, Oxman A, Schunemann H. GRADEPro Version 3.6 for Windows. GRADE Working Group, 2004.

Grant 1992
Grant SM, Faulds D. Oxcarbazepine: a review of its pharmacology and therapeutic potential in epilepsy, trigeminal neuralgia and affective disorders. *Drugs* 1992;**43** (6):873–8.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

ILAE 2009
Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, Moshé SL, Perucca E, Wiebe S, French J. Definition of drug resistant epilepsy. Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2009;**51**(6):1528–1167.

Kang 2012
Kang HC1, Hu Q, Liu XY, Liu ZG, Zeng Z, Liu JL, et al. A follow up study on newer anti-epileptic drugs as add-on and monotherapy for partial epilepsy in China. *Chinese Medical Journal* 2012;**125**(4):646–51.

Kirkham 2010
Kirkham JJ, Swan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:365.

Kwan 2000
Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine* 2000;**342**(5): 314–9.

LaFrance 2008
LaFrance WC Jr, Kanner AM, Hermann B. Chapter 20: psychiatric comorbidities in epilepsy. *International Review of Neurobiology* 2008;**83**:347–83.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from http://handbook.cochrane.org/.

Marson 1997
Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia* 1997;**38**(8):859–80.

Panebianco 2015
Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. *Cochrane Database of Systematic Reviews* 2015, Issue 4. [DOI: 10.1002/ 14651858.CD002896.pub2]

Privitera 1999
Privitera MD. Evidence-based medicine and antiepileptic drugs. *Epilepsia* 1999;**40**(Suppl 5):S47–S56.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan) Version 5.3. Copenhagen. The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sander 1990
Sander JW, Hart YM, Johnson AL, Shorvon SD. National General Practice Study of Epilepsy: newly diagnosed epileptic seizures in a general population. *Lancet* 1990;**336** (8726):1267–71.

Schunemann 2011
Schunemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org*. The Cochrane Collaboration, 2011.

Shorvon 2014
Shorvon S. *Handbook of Epilepsy Treatment*. 2nd Edition. Oxford: Blackwell Science, 2013.

West 2015
West S, Nolan, S, Cotton J, Candhi S, Weston J, Sudan A, et al. Surgery for epilepsy. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/ 14651858.CD010541.pub2]

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Epilepsy Specialized Register search strategy

#1 actinium or barzepin or carbox or deprectal or “gp 47680” or lonazet or ocbz or oxalepsy or oxcarbamazepine or oxcarbazepine or oxetol or oxpin or oxrate or “oxtellar xr” or oxypine or pharozepine or prolepsi or timox or trexapin or trileptal or trileptin
#2 INREGISTER
#3 #1 AND #2
#4 (monotherap* NOT (adjunct* OR “add-on” OR “add on” OR adjuvant* OR combination* OR polytherap*)):TI
#5 #3 NOT #4

Appendix 2. CENTRAL via CRSO search strategy

#1 actinium OR barzepin OR carbox OR deprectal OR “gp 47680” OR lonazet OR ocbz OR oxalepsy OR oxcarbamazepine OR oxcarbazepine OR oxetol OR oxpin OR oxrate OR “oxtellar xr” OR oxypine OR pharozepine OR prolepsi OR timox OR trexapin OR trileptal OR trileptin
#2 (epilep* OR seizure* OR convuls*):TI,AB,KY
#3 MESH DESCRIPTOR Epilepsy EXPLODE ALL TREES
#4 MESH DESCRIPTOR Seizures EXPLODE ALL TREES
#5 (#2 OR #3 OR #4) NOT INMEDLINE
#6 #1 AND #5
#7 (monotherap* not (adjunct* or “add-on” or “add on” or adjuvant* or combination* or polytherap*)):TI
#8 #6 NOT #7

Appendix 3. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2011).
1. (actinium or barzepin or carbox or deprectal or “gp 47680” or lonazet or ocbz or oxalepsy or oxcarbamazepine or oxcarbazepine or oxetol or oxpin or oxrate or “oxtellar xr” or oxypine or pharozepine or prolepsi or timox or trexapin or trileptal or trileptin).tw.
2. exp Epilepsy/
3. exp Seizures/
4. (epilep$ or seizure$ or convuls$).tw.
5. 2 or 3 or 4
6. exp *Pre-Eclampsia/ or exp *Eclampsia/
7. 5 not 6
8. (randomized controlled trial or controlled clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
9. clinical trials as topic.sh.
10. trial.ti.
11. 8 or 9 or 10
12. exp animals/ not humans.sh.
13. 11 not 12
14. 1 and 7 and 13
15. (monotherap$ not (adjunct$ or “add-on” or “add on” or adjuvant$ or combination$ or polytherap$)).ti.
16. 14 not 15
17. remove duplicates from 16

WHAT'S NEW

Last assessed as up-to-date: 8 November 2016.

Date	Event	Description
26 April 2017	Amended	Declarations of interest updated.

CONTRIBUTIONS OF AUTHORS

MO: responsible for developing this protocol.

CFJ: contributed to the development of this protocol

AGM: supervised the protocol process and provided expert opinion and feedback.

DECLARATIONS OF INTEREST

MO: None known.

CFJ: None known.

AGM: A consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to University of Liverpool. Professor Tony Marson is Theme Leader for Managing Complex Needs at NIHR CLAHRC NWC.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This protocol was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Epilepsy Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health.